Topic Discussion - Anticoagulation

Drugs used in clotting disorders

Anticoagulants

Heparins
- Direct thrombin inhibitors
- Direct factor Xa inhibitors

Warfarin

Thrombolytics

t-PA derivatives
- Streptokinase

Aspirin

Antiplatelet drugs

Glycoprotein IIb/IIIa inhibitors
- ADP inhibitors (clopidogrel)
- PDE/adenosine uptake inhibitors

Replacement factors

Vitamin K

Antiplasmin drugs

Drugs that facilitate clotting

Figure 1. (Overview of drug classes from Pharmacology Katzung 12th edition)

Figure 2. (The Role of Antithrombotics in Secondary Stroke Prevention, 2010 Seminars in Neurology)
**Purpose of anticoagulation**
- Treatment and prevention
  - Myocardial Infarction and other acute coronary syndromes
  - Ischemic strokes in atrial fibrillation
  - Deep vein thrombosis (DVT)
  - Venous and arterial thrombosis

**Normal physiology**
- **Zymogen** - enzyme that is an inactive substance that becomes an active enzyme when activated by another enzyme.
- Our body makes protein c and protein s that inactivate factors V and VIII.
  - V is important in activating X.
  - VIII is important in activating IX.
- **Extrinsic → thrombin.**
- **Thrombin (II) will activate V, VII, VIII, XI, XIII.**

**Classes**

**Heparins**

![Diagram of anticoagulant mechanism](image)

**Heparin**
- Large sulfated polysaccharide polymer often obtained from animal sources. On average the batch has a molecular weight of 15,000 – 20,000. Administered IV or SC.
- Dose-dependent clearance → binds to endothelium and plasma proteins → lower dose means shorter half-life binding to endothelium.

**LMWH**
- Has a molecular weight of 2,000-6,000. Mechanism of action: direct binding of factor Xa.
c. Reversal agent → protamine sulfate to neutralize heparin, basic polypeptides that bind with heparin with high affinity, creating complexes, and allowing for clearance. 1mg to neutralize 100 units of heparin.

2. Low-molecular-weight (LMW) fractions of heparin
   a. Enoxaparin (Lovenox®), Dalteparin (Fragmin®)
   b. Molecular weights of 2,000 – 6,000. Higher bioavailability and longer duration of action than unfractionated heparin.
   c. Less binding to endothelial cells and reduced dose-dependent clearance.
   d. Lab monitoring warranted if obese, renal insufficiency, pregnancy (dose requirements change in third trimester), patients with mechanical heart valves, infants/children.
   e. Dosing for enoxaparin for DVT prophylaxis: 30mg SC BID or 40mg daily
      i. Treatment of DVT: 1mg/kg

3. Fondaparinux (Arixtra®)
   a. Small synthetic drug that contains biologically active pentasaccharide present in unfractionated and LMW heparins
   b. Subcutaneously once daily

4. Heparin Induced Thrombocytopenia (HIT)
   a. Antibody-mediated process triggers against neoantigens on platelet factor 4 (PF4) exposed when heparin binds. Antibodies bind heparin-PF4 complex and to platelet Fc receptors → activating platelets and generating microparticles that can bind to clotting factors and promote thrombin generation.
   b. Presentation
      i. Occurs within 5-10 days
      ii. Platelet count of <100,000/uL or a 50% decrease of platelet count
      iii. Venous thrombosis more common than arterial thrombosis
      iv. More common in unfractionated heparin
   c. Diagnosis → enzyme-linked immune-assay to detect antibodies or serotonin release assay (most specific diagnostic test) Quantifies serotonin release when washed platelets loaded with labeled serotonin are exposed to patient serum in absence or presence of varying heparin → more antibody, heparin induces activation and serotonin release.
   d. Treatment
      i. Stop all heparin, give an alternative anticoagulant such as lepirudin, argatroban, bivalirudin, fondaparinux or rivaroxaban.
      ii. Do not give platelet transfusion, do no give warfarin until platelet count returns to baseline. Evaluate for thrombosis

Direct Thrombin Inhibitors
1. Binding directly to thrombin and blocks interaction with substrates
2. Lepirudin (Refludan®) (discontinued) and desirudin (Iprivask®)
   a. Renal cleared
   b. Antibody formation against the drug is highly likely to lepirudin. While desirudin does not create antibodies to the same extent. In some cases, patients with antibodies have an enhanced anticoagulant effect due to decreased clearance. aPTT 1.5-2.5 times the control.
3. Bivalirudin (Angiomax®)
   a. Metabolized by peptidases and quickest shortest half-life
4. Argatroban
   a. Hepatic metabolism
   b. Can affect INR, should be stopped 2-3 hours before INR determination

Warfarin (Coumadin®)
1. Water-soluble vitamin K antagonist interferes with vitamin K-dependent clotting proteins
Anticoagulation 4

a. Prothrombin (factor II), and factors VII, IX, and X. Protein C and S are reduced too.

All the vitamin K-dependent clotting factors have a posttranslational modification adding a carboxyl group to the γ-carbon to generate carboxyglutamic acid necessary for calcium-dependent binding to negatively charged phospholipid surfaces.

Vitamin K turns into oxidized vitamin K (vitamin K epoxide).

Racemic mixture, S-warfarin being the most active. Warfarin to exert its mechanism of action, need to wait. Anticoagulation depends on decrease of factor X and prothrombin (24 and 72 hours half life of clotting factors) at least 5 days of coverage with another anticoagulant is needed.

1. Pharmacogenomics
   a. CYP2C9*2 and C9*3 more common variants 25% of Caucasians have a variant causing a decrease of 20-30% of warfarin dose.
   b. VKORC1 (Asians have a higher prevalence of VKORC1), 30% of the variability of warfarin dose requirements. One amino acid difference causes a change in binding

2. Monitoring is done through the international normalized ratio (INR) was used for standardization → PT/normal PT * ISI. Narrow therapeutic window.

3. Dosing is 5-10 mg minimum 5-day course to have full anticoagulant effect and at least 2 consecutive days of taking warfarin to see an effect on INR.
   a. Stable patients should still be monitored every 3-4 weeks.
   b. 97% of circulating warfarin is bound to albumin.

4. Reversal Agents
   a. If INR is 3.5 and 10 without symptoms, withhold warfarin until INR is in therapeutic range
   b. If INR is above 10, oral vitamin K should be administered as 2.5-5mg.
   c. If symptomatic, 5-10mg of vitamin K should be given as slow IV infusion
      i. Prothrombin complex concentrate should be given that has all four-vitamin k-dependent clotting proteins.
         1. Better normalization occurs compared to infusing with frozen plasma.

2. Skin Necrosis
   a. Common in individuals that have congenital or acquired deficiencies of protein C or protein S.

3. Target goals and ranges depend on the indication
   a. INR 2-3 usually used as target range usually
   b. INR 2.5-3.5 reserved for populations such as those with a mechanical heart valve.
   c. INR 1.8-2.2 is recommended for orthopedic surgeries

Direct Factor Xa inhibitors
1. Shown to prevent stroke primarily driven by the reduction in hemorrhagic stroke, lower mortality, decrease risk of major bleeding, and decrease of intracranial bleeding.
   a. Lower risk of intracranial bleeding likely due to warfarin’s ability to reduce factors VII, which is important in thrombin generation at sites of microvascular bleeding
   b. Higher Gastrointestinal bleeding, unabsorbed active drugs in the GI system exacerbates lesions.
   c. Safe and effective in those over the age of 75 years old and prior history of stroke

2. Loading Dose
   a. Dabigatran and edoxaban was started after a 5-day course of parenteral anticoagulation
   b. Higher initial dose in Rivaroxaban (21 days), apixaban (7 days), betrixaban (1 day)

3. Monitoring
   a. PT can be used for Xa and aPTT for dabigatran.

4. Management of bleeding
   a. Holding one or two doses is usually sufficient for reversal.
   b. Idarucizumab (Praxbind®) = reversal for dabigatran
   c. Andexantra (Andexxa®) = reversal for rivaroxaban and apixaban

References
a. Monitoring by: activated partial thromboplastin time (aPTT)
   iii. Receive selica or kilica PTT → 35 seconds
   iv. PTT intrinsic and common vs PT extrinsic
   v. Unneeded lab monitoring fix dose of 5000 units SC two or three times daily

5. Monitoring through prothrombin time → sensitive to prothrombin, VII, and X. Time to clot formation. Thromboplastin is the reagent that has tissue factor, phospholipid, and calcium. Depends on what thromboplastin you used. INR was used for standardization → PT/normal PT * ISI. Narrow therapeutic window. International sensitivity index

K centra

American academy of orthopeadic surgeons and chest practice guidelines

Phytoanadione manaquinon → mephyton